

The following is a complete listing of all claims in the application, with an indication of the status of each:

Listing of claims:

1. (Currently amended) A method of detecting, using a computer, an interaction among agents in a group or mixture using a fixed- ratio ray design and determining whether subsets of said agents also interact, in order to detect, characterize or predict an outcome caused by exposure to said agents in said_ group or mixture, comprising the steps of

a) determining, using said computer, an additivity model from single chemical dose-response data for said agents in said_ mixture or group, wherein said single chemical dose-response data is obtained in test subjects;

b) fitting, using said computer, a mixture model in terms of total dose to mixture dose-response data from fixed-ratio rays for said agents in said_ group or mixture, wherein said mixture data is obtained in test subjects;

c) statistically comparing, using said computer, said additivity model to said mixture model to detect a departure from additivity, wherein a difference between said additivity model and said mixture model indicates an interaction among said agents in said group or mixture;

d) removing, using said computer, ~~at least one~~ a subset of agents from said group or mixture, wherein relative ratios of amounts of agents remaining agents in said group or mixture

stay the same as in said fixed-ratio ray design such that $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$ where $a_{i(full)}$ is a proportion of the i^{th} chemical in said group or mixture, $a_{j(full)}$ is a proportion of the j^{th} chemical in said group or mixture, $a_{i(reduced)}$ is a proportion of the i^{th} chemical in said remaining agents, and $a_{j(reduced)}$ is the proportion of the j^{th} chemical in said remaining agents;

e) repeating steps b and c for agents remaining in said group or mixture after removal of said subset; and

f) determining, using said computer, whether or not said agents remaining agents in said group or mixture interact with said subset of agents by utilizing statistical hypothesis testing

using said full and reduced ray mixture models, in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture; and

g) providing results obtained in step f in the form of a plot or table.

2. (Original) The method of claim 1 wherein said method is applied to a plurality of full-ray groups.

3. (Original) The method of claim 1 further comprising the step of carrying out steps b and c for said subset of agents.

4. (Original) The method of claim 1, wherein said additivity model is graphically represented as an additivity curve and said mixture model is graphically represented as a mixture curve in terms of total dose.

5. (Currently amended) The method of claim 1, further comprising the step of determining, using said computer, simultaneous confidence bands on the difference between said additivity curve and said mixture curve or between mixture curves on full and reduced rays.

6. (Currently amended) A method of detecting, in a group or mixture of agents, using a fixed-ratio ray design, the number of agents that interact, and determining whether subsets of said agents also interact, in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture, wherein said method is carried out using a computer, said method comprising the steps of

a) fitting, using said computer, a suitable polynomial in total dose to experimental dose-response data obtained with a combination of said agents said experimental data is obtained in test subjects;

b) statistically identifying, using said computer, higher order terms of said polynomial that are not equal to zero, wherein the number of agents that interact in said group or mixture of agents is equal to the degree of said higher order terms that are not equal to zero;

- c) removing, using said computer, at least one subset of agents from said group or mixture, wherein
relative ratios of amounts of remaining agents stay the same as in said fixed-ratio ray design such that $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$ where $a_{i(full)}$ is a proportion of the i^{th} chemical in said group or mixture, $a_{j(full)}$ is a proportion of the j^{th} chemical in said group or mixture, $a_{i(reduced)}$ is a proportion of the i^{th} chemical in said remaining agents, and $a_{j(reduced)}$ is the proportion of the j^{th} chemical in said remaining agents;
- d) repeating steps a and b for agents remaining in said group or mixture after removal of said subset;
- e) determining, using said computer, whether or not said remaining agents interact with said subset of agents by utilizing statistical hypothesis testing using said full and reduced ray mixture models, in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture; and
- f) providing results obtained in step e in the form of a plot or table.

7. (Original) The method of claim 6 wherein said method is applied to a plurality of full-ray groups.
8. (Original) The method of claim 6 further comprising the step of carrying out steps a and b for said subset of agents.
9. (Original) The method of claim 6, wherein single chemical data are used to estimate an additivity model which is linked to a linear term in said polynomial model.
10. (Original) The method of claim 9, wherein an additivity model is graphically represented as an additivity curve and said polynomial model is graphically represented as a mixture curve in terms of total dose.

11. (Original) The method of claim 6, wherein said polynomial is embedded in a generalized linear model.

12. (Original) The method of claim 6, wherein said polynomial is embedded in a general non-linear model.

13. (Original) The method of claim 6, further comprising the step of generating a graphical representation of said polynomial in total dose.

14. (Currently amended) A method of determining, using a computer, an interaction threshold boundary for agents in a group or mixture in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture, comprising the steps of

generating, using said computer, a generalized linear model or general nonlinear model that permits estimation of the boundaries between a region of additivity of said agents and a region of interaction of said agents, wherein ~~said generalized linear model and said general nonlinear model are represented by—~~

$$g(\mu) = \left[\begin{array}{l} \beta_0 + \sum_{r=1}^c \beta_r x_r, \quad x_c \leq Q(x_1, x_2, \dots, x_{c-1}) \\ \beta_0 + \sum_{r=1}^c \beta_r x_r + \sum_{r=1}^{c-1} \sum_{s=r+1}^c \beta_{rs} x_r x_s + \\ \sum_{r=1}^{c-2} \sum_{s=r+1}^{c-1} \sum_{u=s+1}^c \beta_{rsu} x_r x_s x_u + \quad x_c > Q(x_1, x_2, \dots, x_{c-1}) \\ \dots + \beta_{12\dots c} x_1 x_2 \dots x_c \end{array} \right]$$

or by

$$\left[\begin{array}{l} \beta_0 + \sum_{r=1}^c \beta_r x_r, \quad x_c \leq Q(x_1, x_2, \dots, x_{c-1}) \\ \beta_0 + \sum_{r=1}^c \beta_r x_r + \sum_{r=1}^{c-1} \sum_{s=r+1}^c \beta_{rs} x_r x_s + \\ \sum_{r=1}^{c-2} \sum_{s=r+1}^{c-1} \sum_{u=s+1}^c \beta_{rsu} x_r x_s x_u + \quad x_c > Q(x_1, x_2, \dots, x_{c-1}) \\ \dots + \beta_{12\dots c} x_1 x_2 \dots x_c \end{array} \right]$$

embedded in a general nonlinear model, respectively;

and said boundaries define said interaction threshold boundary, and wherein said step of generating is carried out in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture; and

providing results obtained by said method in the form of a plot or table, wherein said region of additivity of said agents and said region of interaction of said agents is determined by the steps of

a) determining, using said computer, an additivity model from single chemical data for said agents in said mixture or group, wherein said single chemical data is obtained in test subjects;

b) fitting, using said computer, an interaction threshold mixture model that incorporates an interaction threshold parameter in terms of total dose to mixture data from fixed-ratio rays for said agents in said group or mixture, wherein said mixture data is obtained in test subjects; and

c) statistically comparing, using said computer, said additivity model to said interaction threshold mixture model to detect a departure from additivity, wherein a region of difference between said additivity model and said interaction threshold mixture model indicates a region of interaction among said agents in said group or mixture, and a region of coincidence between said additivity model and said interaction threshold mixture model indicates a region of additivity among said agents in said group or mixture;

d) removing, using said computer, at least one subset of agents from said group or mixture wherein relative ratios of amounts of remaining agents stay the same as in said fixed-

ratio ray design such that $\frac{a_{i(\text{full})}}{a_{j(\text{full})}} = \frac{a_{i(\text{reduced})}}{a_{j(\text{reduced})}}$ where $a_{i(\text{full})}$ is a proportion of the i^{th} chemical in said group or mixture, $a_{j(\text{full})}$ is a proportion of the j^{th} chemical in said group or mixture, $a_{i(\text{reduced})}$ is a proportion of the i^{th} chemical in a subset of remaining agents, and $a_{j(\text{reduced})}$ is the proportion of the j^{th} chemical in said remaining agents;

e) repeating steps b and c for agents remaining in said group or mixture after removal of said subset;

f) determining using said computer, whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray interaction threshold mixture models; and

g) providing results obtained in step f in the form of a plot or table.

15. (Cancel)

16. (Currently amended) The method of claim +5 14 wherein said method is applied to a plurality of full-ray groups.

17. (Cancel)

18. (Currently amended) The method of claim +5 14 further comprising the step of carrying out steps b and c for said subset of agents.

19-25. (Cancel)

26. (Previously presented) The method of claim +5 14, wherein single chemical data are also utilized, wherein said single chemical data is obtained in test subjects.

27-38. (Cancelled)